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A Model for Radiating Leg Pain of Endometriosis

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Abstract

Endometriosis is a prevalent female health disorder that often leads to back pain and radiating leg pain. Patients with such pain often seek care from multiple health care professionals, including manual therapists. We hypothesized that endometrioma can induce nerve inflammation thus the radiating leg pain that often accompanies endometriosis. To model sciatic endometriosis in female Wistar rats, a section of uterine horn was autotransplanted to the sciatic nerve. Uterus sections with the endometrium removed and autotransplanted to the sciatic nerve served as controls. After 1, 3, and 15 months the nerves were harvested and processed for immune cell presence and for neural elements. Control nerves were harvested after 4 months. All autotransplants survived, resulting in a fusion of the uterus sections to the nerves. Macroscopically, turgid cysts apposed to the nerves characterized the complexes. Microscopically, the complexes contained recruited macrophages, indicating persistent inflammation, and were innervated by small diameter axons. Only 1 of 8 control rats developed a small cyst, presumably due to residual endometrium. The persistent immune response and innervation suggest the nerve-uterus complexes as sources of inflammation and persistent neural discharge, and thus pain. This model could shed light upon the radiating leg pain that often accompanies endometriosis. Manual therapists should be aware of the possibility of endometriosis causing symptoms and examination findings that mimic musculoskeletal etiologies.

Keywords

endometrium; sciatic nerve; pain; rat; autotransplant

Introduction

Endometriosis is defined by the presence of tissue resembling endometrium external to the uterus, and is associated with infertility, dysmenorrhea, and chronic pelvic pain (Attaran et al., 2002; Berkley et al., 2005; Giudice & Kao, 2004; Halis & Arici, 2004). Although prevalent, endometriosis remains neither readily diagnosed (Hadfield et al., 1996) nor easily treated (Attaran et al., 2002).

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Radiating leg pain related to the menstrual cycle has been reported as a complication of endometriosis in a number of case studies (Baker et al., 1966; Bjornsson, 1976; Denton & Sherrill, 1955; Floyd et al., 2011; Forrest & Brooks, 1972; Head et al., 1962; Motamedi et al., 2015; Pacchiarotti et al., 2013), and in two surveys (Missmer & Bove, 2011; Walch et al., 2014). A consistent and thus perhaps key diagnostic feature seems to be the cyclical or catamenial nature of the symptom, especially earlier in the progression of the endometriosis (Capek et al., 2016; Dhote et al., 1996; Moeser et al., 1990; Takata & Takahashi, 1994; Zager et al., 1998). However, the symptom duration usually expands with endometriosis progression, developing into constant pain if left untreated.

Examination findings in women with leg pain due to endometriosis are typical of sciatica due to other causes (Torkelson et al., 1988), including painful straight leg raising testing, and may also include a diminished Achilles tendon reflex, mild muscular atrophy, and tenderness of the sciatic nerve at the sciatic notch. Lumbar spinal investigations (myelogram, CSF analysis) are usually unremarkable, but magnetic resonance imaging can demonstrate larger lesions (Binkovitz et al., 1991; Cottier et al., 1995; Yekeler et al., 2004).

Surgical descriptions of sciatic endometriosis describe inflammatory lesions that involve surrounding structures that are not necessarily otherwise diseased (Descamps et al., 1995; Yekeler et al., 2004). In an animal model, it has been shown that a focal inflammation of the sciatic nerve (called sciatic neuritis) evokes mechanical sensitivity in the axons of a subset of nociceptive (potentially pain-evoking) neurons without causing overt nerve damage (Bove et al., 2003; Dilley & Bove, 2008; Dilley et al., 2005). Furthermore, the sheaths of nerve trunks are innervated by mechanically and chemically-sensitive nociceptors (Bove & Light, 1995a, b, 1997), which also participate in maintaining the local environment of the nerve (Sauer et al., 1999). These findings suggest that inflamed nerves are a source of pain perceived as coming from the nerve and as coming from the structure(s) that the nerve innervates. We hypothesize that such a mechanism of radiating pain generation is also involved in endometriosis. To investigate this possibility, a rat model was designed based upon the common rat model of endometriosis, where a section of uterus is autotransplanted to other intraperitoneal structures (Golan, 1987; Sharpe-Timms, 2002; Vernon & Wilson, 1985). Here we report initial observations of a model, in which a section of uterus was autotransplanted to the sciatic nerve. A similar model has recently been published which demonstrated behavioral hypersensitivities and increased afferent drive (Chen et al., 2015).

Methods

All experiments adhered to the guidelines of the Committee for Research and Ethical Issues of the International Association for the Study of Pain, and were approved by the Animal Care and Use Committee of the University of New England. Adult female Wistar rats were anesthetized using isoflurane in pure oxygen (4% for induction, 1.75 – 2.25% for maintenance). All survival surgeries were preformed using aseptic methods. The skin of the abdomen was shaved and scrubbed with an iodine solution followed by 70% isopropyl alcohol. A 2 cm incision was made in the abdominal skin and then through the abdominal musculature. The uterine fat pad was grasped and exteriorized to identify the right uterine horn. A 1 cm section of the distal third of the horn was isolated using 2 ligations, and small

vessels were ligated. The uterine section was removed and placed in oxygenated synthetic interstitial fluid (Bretag, 1969). After assuring hemostasis, the incision was sutured in layers, and dusted with an antibiotic powder. To access the sciatic nerve, the left thigh was shaved and scrubbed with an iodine solution and 70% isopropyl alcohol. A 2 cm incision was made parallel and just posterior to the femur. The femoral insertion of the biceps was cut and the soft tissues retracted to reveal the sciatic nerve. The sciatic nerve was freed from surrounding tissue under microscopic observation without causing bleeding or other observable nerve damage. The uterus section was slit open along its long axis and trimmed to 6 - 7 mm in length, placed around the nerve like a cuff, and the edges gently approximated using 2 7-0 nylon sutures, using great care to not constrict the nerve (i.e., the cuff remained mobile). For controls, the endometrium was sharply removed from the longitudinally split uterus section under microscopic observation, and the section, devoid of endometrium, was applied to the nerves in the same fashion. The muscles and skin were closed with interrupted absorbable sutures and dusted with an antibiotic powder. Rats were moved to a warmed cage and allowed to recover. Buprenorphine was given (0.05 mg/kg s.c.) for pain control 20 minutes prior to closure of the leg and every 12 hours for 48 hours.

At 1 (n = 4), 3 (n = 6), and 15 (n = 6) months post-surgically for full uterus autotransplants, and at 4 months (n = 8) for endometrium-devoid uterus autotransplants, animals were given an intraperitoneal overdose of pentobarbital or ketamine/xylazine, and transcardially perfused with phosphate buffered saline. Some complexes were photographed *in situ*. The affected nerves, contralateral nerves, and sections of normal uterus were removed, aligned in embedding medium, and flash frozen in dry ice-chilled 2-methybutane. Cross sections were cut at 8 μ m with a cryostat, thaw-mounted on slides, and fixed with 4% paraformaldehyde in 0.1% phosphate buffered saline for 7 minutes. After drying for at least 1 hour and rinsing for 10 min with dH₂O, sections were stained with H & E or processed for immunoreactivity using standard ABC methods (Elite ABC kit, Vector Laboratories, USA) to demonstrate the presence of immune cells and nerve fibers. Primary antibodies included anti-ED1 (for recruited macrophages; Serotec, USA; 1:250), anti-ED2 (for resident macrophages; Serotec, USA; 1:1000), anti-TCR $\alpha\beta$ (for activated T-cells; BD Pharmingen, USA; 1:25), and anti-peripherin (a nerve-specific cytoskeletal protein; Chemicon, USA; 1:10,000). Secondary antibodies included goat anti-mouse (ED-1, ED-2, and TCR $\alpha\beta$; 1:500) and goat anti-rabbit (peripherin; 1:300, Jackson Laboratories, USA). Immunohistochemical controls were performed using no primary antibody. Slides were viewed and photographed using a Nikon microscope fitted with a SPOT digital camera, and processed for resolution and size using Adobe Photoshop with no additional modifications.

Results

All rats recovered from the surgeries without complication. In all experimental animals, cysts were found apposed to or surrounding the nerves. The cysts were turgid and filled with straw-colored translucent fluid, and ranged in size from 5 - 12 mm in diameter (Fig. 1A). H & E staining revealed that the cysts were essentially normal uterine tissue, fused with apparently normal nerve (Fig. 1B). In most cases, the tissue had retracted to lie beside the nerve, as is shown in the example.

The peripherin antibody revealed a network of axons located between the nerve and the uterus (Fig. 2A). The axons were of various diameters, including larger diameter axons as well as small diameter axons (Fig. 2B).

All sections from the complex revealed numerous macrophages (Fig. 3A-B), and some T-cells (Fig. 3C). ED1-positive macrophages, which are recruited during inflammation, were located at the nerve uterus interface, and more interestingly, within the nerve, indicating that they had crossed the blood-nerve barrier (Fig. 3A). ED2-positive macrophages (resident) were observed within the uterine tissue, like in normal uterus (Fig 3C), and between the nerve and uterus (Fig. 3B). Quantification of the cell numbers was not attempted. No control slides showed specific ED1, ED2, or T-cell labeling.

Discussion

We have demonstrated that uterine tissue transplanted to a peripheral nerve will survive, becoming vascularized and innervated. Apparently, a level of immune mediated inflammation persists at least to 15 months, which is a large part of the life span of a laboratory rat. Because neuritis in humans is painful (Brown, 1828; Hadden & Hughes, 1999; Moalem & Tracey, 2006), we conclude that these lesions were likely painful. Similar appearing nerve-endometrioma complexes were reported in human endometriotic biopsies, and seem likely to be involved in the pain of endometriosis (Anaf et al., 2000).

The appearance resembles the cyst formation in the intraperitoneal model of endometriosis (Berkley et al., 2004; Golan, 1987; Sharpe-Timms, 2002; Vernon & Wilson, 1985). Formation of smaller but otherwise similar looking cysts is only occasionally seen in the complete Freund's adjuvant neuritis model, which induces inflammation but no damage to the axons (Bennett & Xie, 1988; Wallas et al., 2003), but only during the first week following surgery. Such cysts have never been observed following various sham operations, the chronic constriction injury model, following application of incomplete Freund's adjuvant or carageenan to the nerve, or following placement of a silastic pellet close to the nerve (Wallas et al., 2003). These other models are important for comparison as they suggest that that such chronic cyst formation is unique in the nerve pathology models studied to date.

It remains a speculation that the rats in this study had radiating leg pain. This is a methodological limitation in that there is not an appropriate test to determine if rats have the type of pain which humans with deep radiating pain report: patients who report radiating leg pain do not usually report cutaneous pain at rest or when provoked (Bove et al., 2005; Murphy et al., 2009), and, perhaps more importantly, patients with radiating limb pain do not report tenderness in the area of the pain (unpublished clinical observations). Since the common tests used for some pain conditions in rats use only cutaneous stimulation (von Frey filaments, thermal stimuli), such testing, even if positive, would be difficult to interpret.

The most interesting finding in these studies is the neo-innervation, which strongly supports that the complex is a potential source of sensation. When a section of tissue is removed from the body, the sensory axons within it die and degenerate, since they have been cut from their cell bodies. However, like human and modeled rat endometrioma (Berkley et al., 2004;

Berkley et al., 2005), the complexes became innervated. The source of these axons is unknown, and could be collateral sprouts from intact axons, sprouts from damaged axons, or a proliferation of axons that normally innervate the nerve sheaths (Bove & Light, 1997)). This is a topic for further study. Pain is a likely mode of the resulting sensation, especially since many of the axons were small diameter and contained peripherin.

Inflammatory cells release inflammatory cytokines and chemokines that can be noxious (Ainsworth et al., 1996; Djaldetti et al., 2002), and which could in themselves lead to sensory neuron discharge of the newly formed neural elements and also of intact axons that are passing through the complex (Leem & Bove, 2002; Sorkin et al., 1997). However, the presence of immune cells within the perineurium indicates the presence of some other factor in the nerve-uterus complex in comparison to the neuritis model, where no immune cells cross the perineurium although the inflammation is far more pronounced (Bove et al., 2003). It is possible that the complex formation damages axons in the sciatic nerves. Such damage leads to degeneration that is effective for immune cell recruitment, and was reported to increase activity in nociceptive afferent neurons (Dilley & Bove, 2008; Djouhri et al., 2006; Wu et al., 2002). Neural activity caused through this mechanism would be perceived as pain in the innervated area (i.e., distally, in the leg).

The mechanism of pain generation in endometriosis remains unclear. Current proposed mechanisms include the recent observation that in a rat model and in humans, experimental endometrioma become innervated, i.e., nerves grow into the experimental endometrioma (Berkley et al., 2004; Berkley et al., 2005). In addition, human pelvic adhesions become innervated (Sulaiman et al., 2001). These findings allow the possibility that endometrioma and subsequent adhesions become a source of neural discharge that generates pain symptoms. Here we add the possibility that nerve inflammation and possibly axonal damage induced by endometriosis may be a key mechanism of the pain associated with endometriosis. Nerves innervating abdominal and pelvic organs as well as much of the lower limb pass through the abdomen and are potentially exposed to endometrioma, which seem to have a predilection for nerves (Anaf et al., 2004; Anaf et al., 2000). If affected, symptoms would be perceived as coming from the nerve and also from the nerve's more distal target. Pain drawings made by women with endometriosis and leg pain support the concept that other nerves are potentially affected (Missmer & Bove, 2011).

Conclusion

Our survey and another report indicate that leg pain affects about half of patients with endometriosis (Missmer & Bove, 2011; Walch et al., 2014), but the relative paucity of published accounts suggests that the link between the two may be under-recognized. Also, since the symptoms are quite similar to those that can be attributed to lumbar intervertebral discal pathology and other musculoskeletal pathologies, misdiagnosis seems likely. All health care providers need to remain aware of endometriosis as a possible etiology of musculoskeletal symptoms. Our new model reproduces the pathological presentation of radiating leg pain with endometriosis. Future studies using this new model may help shed light on the basic mechanisms of radiating pain due to endometriosis, and may also increase clinical awareness of the possible nerve involvement in endometriosis.

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Figure 1.

The rat nerve-uterus complex as a model of sciatic endometriosis. A. Cyst (long arrow) on sciatic nerve (short arrow), 15 months after operation. Scale bar = 10 mm. B. H & E staining demonstrated that the drained cyst was uterus (arrow indicating endometrium) attached to the nerve (asterisk). Scale bar = 500 μ m. C. Normal rat uterus, H & E staining (arrow indicating endometrium). Scale bar = 200 μ m.

Figure 2.

Peripherin immunohistochemistry demonstrated neo-innervation of a nerve-uterus complex (15 months post-operatively). A. Large diameter fibers (short large arrow) and small diameter axons (box) are seen in the uterine transplant. Asterisk = nerve, small arrow = uterus, scale bar = 200 μ m. B. Enlargement of box from A shows small diameter axons apparently with terminal boutons (arrow). Scale bar = 50 μ m.

Figure 3.

Immunohistochemistry for immune cells in a rat nerve-uterus complex. All photographs were taken from different sections of the same complex, at slightly different levels. Black dots are stained cells in all photographs, asterisk = nerve, arrow = uterus. A. ED1 labeled macrophages were recruited primarily into the connective tissue between the uterus section and the nerve, and some appeared within the nerve. B. ED2 labeled macrophages (resident) were observed primarily in the uterus. C. TCR $\alpha\beta$ labeled T-cells were recruited sparsely to the uterus, but not into the nerve. Scale bar = 200 μm .